guess we really haven't--I think we are all accepting that you can pace through these ablation catheters, and you can record electrograms, the data haven't been presented for that, but that is a claim that is being made here. Do we accept that on face--

DR. SIMMONS: I am not sure what you are saying actually.

DR. TRACY: The summary of safety and effectiveness, one of the intentions was, I think, one thing that we were to be looking at was the ability to pace and record through this thing, and I think that we can, but unless there is some additional information that somebody has, I guess we just assume on faith that you can do that.

DR. SIMMONS: I guess one point that we didn't talk about is on that page 6.3.2-33 is the catheter complaints, and a couple pages later is the number of catheters that broke, and we didn't really address that, but there were 169 complaints out of 315 catheters, and 91 catheter problems, 91 catheters that had a problem out of 315. A lot of these have been addressed, but still that is a lot of technical problems related to pacing, sensing, noise, clearlock failures, bull wire failures, things like that. We didn't address those asking the company.

DR. TRACY: Can we ask that?

DR. SIMMONS: No, you can't come back.

DR. STUHLMULLER: Procedurally, at the end of the panel discussion, the sponsor has the ability to respond to the panel's questions and concerns, and also the FDA at that point has an opportunity to comment, as well.

DR. VETROVEC: This may be somewhat of a procedural question. When I look at the indications and usage and what we are approving is safety and efficacy for this indication and usage, this is a very generalized indication for what we have now defined as a fairly specific use based on this study, that is, for patients with intractable VT in which we are trying to improve the quality of life, and I guess is this the time to address the actual indication statement relative to how we approve it. Maybe that is what I need help on.

DR. SIMMONS: I would think so.

DR. STUHLMULLER: In other words, one approach is, you know, you have a series of questions that were posed. You can systematically go through those, because there are a number of issues related to the labeling.

You have the opportunity to propose a change to the labeling and then make a recommendation based on a revision to the labeling. Does that answer your question?

DR. TRACY: I think as it is stated, the indication for use on page 2-1 in the proposed labeling is very broad compared to the information that we do have. It

just talks about again cardiac electrophysiologic mapping and delivering of diagnostic pacing stimuli, which we have no data, but we are accepting since you can do that through any standard ablation catheter, we are accepting that.

And for radiofrequency ablation of ventricular tachycardia is attributable to ischemic heart disease or cardiomyopathy, I think that that is a little bit broader than the patient population that was included in this study, and I think it opens the door to the possibility of using the drug and exposing the patients to maybe suboptimal care, and that they may not have devices implanted, wouldn't they be better off by other criteria having a defibrillator device implanted.

I wonder what the other panel members feel about just leaving the indication and usage that broadly stated without putting some kind of caveat on there that other information would suggest that if you have a low EF, if you have ischemic heart disease, and so on, and so forth, that you will be better served by having a defibrillator.

DR. VETROVEC: Question 7 to the panel has the proposed alternative indications for usage, which is sort of what I am going to as to what order do we address this. It seems to me that my decision about approval is partly based on what it is approved for.

DR. TRACY: Just adding the statement,

"attributable to ischemic heart disease or cardiomyopathy in patients who have failed drug therapy," adding that statement. I guess I would wonder, is that enough or should there be some additional statement pertaining to the use of implantable devices?

It is just that so many of these patients ended up having defibrillations or recurrences of clinical VT that they had failed drug, but then again if they didn't have the defibrillator, where would they be?

DR. SIMMONS: It has been proposed that we do this in a manner that is more helpful to the FDA, and start with the questions for the panel and work our way through, so, let's start with the questions for the panel.

Do the data presented permit assessment of the safety and effectiveness of this device?

I guess the question is not are we going to vote yes or no, the question is, is there enough data here to make a judgment on whether or not we want to make a judgment.

So, are you willing to say that there is enough data here that we are going to make a judgment? I would say, in my own opinion, yes, there is enough data here to make a judgment one way or another.

Does anybody want to argue with that?

DR. TRACY: My opinion would be there is enough

information presented here to make a judgment on the safety and effectiveness of the device.

DR. SIMMONS: Were the inclusion and exclusion criteria as defined in this study appropriate to allow the safety and effectiveness evaluation of the Cooled Ablation System?

DR. TRACY: Yes, I would say yes. This was a study certainly looking at a very sick patient population, evaluating it sort of in people who were at high risk, and yes, I think that the inclusion/exclusion criteria were reasonable to capture people who would give that information.

DR. SIMMONS: I guess I would say yes with the subheading that, you know, VT is a very complex disease with lots and lots of different etiologies and outcomes, and given for the patient population they are describing, we can talk, but I am uncomfortable talking about other--

DR. TRACY: Such as a structurally normal heart and do you really need that deep of a lesion for an RVOT VT, or a structurally idiopathic LV VT, do we really need lesions that are that large.

DR. SIMMONS: Okay. Let's go on to No. 3 then.

This study included four patient cohorts who received RF ablation, randomized, non-randomized, control crossover, and compassionate use. Is it appropriate to pool

all of the patient cohorts together when evaluating the effectiveness of this device? If not, which is the appropriate cohort to use?

DR. TRACY: I would throw out that crossover group. It leaves you without a control. Essentially, this study lost half of its control within a short period of time. To cross a patient over, you couldn't cross over the other way, so it was a one-way, if that makes any sense, it was a unidirectional crossover. You couldn't unablate something.

So, it is not really providing a control, I don't think, and I think that one of the investigators suggested that you are taking within your control population the sicker people and leaving the healthier people, then, as your final control, and that may be true, but it also leaves you with a very tiny control population to continue following.

I don't think I would have set it up that way to allow that in there, and I think I would probably eliminate that group. From analysis, I don't think it would make a whole lot of statistical difference, though, but I just don't like that.

DR. BRINKER: The randomized cohort is 55 percent chronic success, and combined with the crossover, it is 56 percent, and I think the real argument is that you need the

pooled data for safety, and the effectiveness is well judged on randomized cohort as anything, I think.

DR. SIMMONS: I don't know whether we are arguing here. The question is for effectiveness, so for effectiveness, you don't need the crossover data.

DR. BRINKER: You don't need anything but the randomized, but because everything was so otherwise equal, it shouldn't have been a specific question. I mean it doesn't make any difference. You need the pooled data anyway for safety, and for effectiveness, it is meaningless, you don't need anything but the randomized cohort, but since there is no real discrepancy, it shouldn't matter.

DR. TRACY: There is no real difference. I guess what is effective though, what is the definition of effective?

DR. BRINKER: Their definition of chronic success. I mean there was acute success of the procedure, and there is chronic success, and they analyzed it a number of different ways when they looked at the pooled data. They analyzed their effectiveness excluding patients who had crossed over and including only the randomized data.

We are spending too much time on this question. We don't need anything but the randomized data for effectiveness, but we need the pooled data for safety.

DR. TRACY: But we do lose a lot by having lost

half of the cohort, the control cohort, in evaluating effectiveness. That is my only point on that, but that is the way it is.

DR. BRINKER: We have lost a lot when you decided to randomize 3 to 1 instead of 1 to 1. We understand all that, but is there enough there to look at effectiveness, and intuitively, if the major form of effect, after all is said and done, what we are taking as effectiveness, what we are taking as the benefit is a reduction in VT density, and that really is not reflected by this data, because this data is recurrence of any, one VT, right, and you are failed, which is really we don't want that. That is not our measure of effectiveness.

Our measure of effectiveness is in terms of patient benefit, is does it statistically and meaningfully, significantly numerically and significantly clinically reduce a morbidity for the patient, which is VT, and that is a quantitative analysis. It is not a digital analysis. It is not yes or no, they have VT, it is do they have 40 episodes of VT in two months or do they have 3 episodes.

DR. SIMMONS: But still it is an important question. I mean it is good data to have.

DR. BRINKER: It is good data to have, but not necessary for this.

DR. SIMMONS: Can we agree to just leave out the

crossover because it doesn't help or hurt? I would say yes, just leave it out, it is sort of an aberrant number.

I guess I would disagree that the sickest patients always cross over. I mean I don't know. I mean you get a lot of patients who are very well, that are having recurrent episodes of slow VT that could have been patients that crossed over. I am not sure that we have even established that.

DR. BRINKER: I have one question that keeps poking its head up in this data. Am I assured that the only situation in which one proposes this device to be used is in VT that can be mapped? That is intuitively necessary to do the ablation, so that some of this data includes patients that were enrolled that couldn't be mappable.

All the crossovers presumably were mappable, right, otherwise they would not have crossed over? So, we are dealing with sort of different denominators, and the end game here is that every VT that gets ablated has to be mappable, and I guess in some way that should reflect somewhere down the line in the indications for use, that the VT must be mappable, because it doesn't say that actually in the indications.

DR. VETROVEC: That really was my basic point in saying the question of whether it is approvable for use is really based on what you define it as, and I think they have

shown that it is effective in what we have defined as decreasing the density of ventricular tachycardia, presumably improving quality of life, but the definition of what patient population that occurred in is the really important thing to me in defining the indication.

I am satisfied, and I think some of the things we are arguing over, about which group ought to be included, are probably not quite as pertinent as it is to come to grips with what group really benefitted.

DR. TRACY: Right. From the outset, the primary endpoint was the clinical recurrence of any VT, and that was probably the wrong outcome to have as the primary endpoint given what has been learned from the protocol, but an induction of mappable VT, I think we are sort of stuck with saying are we happy with the outcome of saying that there is less clinical VT, are we happy saying that, of course, you will only ablate things that you can map, and are we going to end with those statements somehow coming to a reconciliation of what this thing will be indicated for, to summarize our concerns here.

DR. BRINKER: The answer is we are happy.

DR. SIMMONS: We are happy.

No. 4. What is the appropriate control to use when evaluating the effectiveness of the Cooled Ablation System as compared to alternative practices - patients

randomized to drug therapy; data from the medical literature for patients taking antiarrhythmic drugs; or patients acting as their own control (no recurrence of VT events in six months)?

DR. TRACY: I think we have all said that the correct control group would have been against the standard ablation system, but we don't have that.

DR. SIMMONS: Given that, I mean I guess I am pretty unhappy with the randomized to drug therapy group. I mean I think that is a major hodgepodge of patients with some I.V. amnio that got stopped and some got started, some drugs were started and some were stopped, and some started in the middle and crossed over. I mean the drug therapy group is lost.

The data from the medical literature on patients taking antiarrhythmic drugs, I guess would be my second choice. I think patients using their own control would be my pick.

DR. BRINKER: I disagree a little bit because remember, according to the entrance criteria, it had to be that patients failed--at least the original entrance criteria is they had to fail two drugs, was it, or whatever?

DR. SIMMONS: The original for nine patients.

DR. BRINKER: Right, but there was still some drug failure for all the indications, maybe not two drugs, but

they had to fail drugs. So, I think that it would be inappropriate to say, well--the best study would have been taking patients' first episode of VT somehow before they were on any drug, randomizing to drugs versus this kind of strategy, and then see what happened, how many need drugs, how many you completely wipe out.

That must be a difficult patient cohort to find because almost everybody that presents at a community hospital with a VT would probably be placed on something before they get to a specialized center.

You know, I think that we--look, from my own take on this--

DR. SIMMONS: These question come on later on. I mean in the back of the panel packet, there are questions for future therapies.

DR. BRINKER: But the future therapies are going to be easy because in the future, if this is approved for VT with this scenario, another company will either have to control with this catheter or they will have to do a control against drug as in every other kind of--you know, until there is some experience with performance criteria for this.

DR. SIMMONS: That is what we can talk about because I don't know that that is true. I am not sure that you couldn't have used VT incidence for three months prior to ablation, and then VT incidence three months after, or

six months before and six months after or something for the next study that comes along, and that might not have been a better study as we are saying here. You know, the number of episodes of clinical VT that affect quality of life may be a more important study than trying to prevent VT completely.

We can argue about that later.

DR. BRINKER: In future studies--

DR. SIMMONS: We can argue about that later.

DR. BRINKER: But you have the data pre- and post-ablation here for the entire group of people, I would guess even the non-randomized people, so that you do have that data. I think what they did was probably the best that they could have done. I don't think that doing a non-cold tip ablation study--it would have been a triple-arm study which would have been a nightmare because we still wouldn't have known whether the central question--you know, in my take, not the electrophysiologist, the question to me is, is ablation of ventricular tachycardia any additional benefit at all to drugs and ICD.

DR. SIMMONS: The way this particular study was designed.

DR. BRINKER: That was the question to me before this study, since there is no data that I am aware of that says the standard for ventricular tachycardia, standard therapy is ablation. I know it is carried on, but I don't

know that that is accepted, Dr. Wilber's comments aside, accepted practice.

But this sets the stage for me. This puts some justification for this approach to me, and for that, it is more potent than registries or 30 patients from this guy or 30 patients from another guy, and I think, as weak as you might think this is in terms of total applicability, this sets a straw man at least that this is what my expectations are for this particular patient population, and of some benefit in terms of symptomatic events and defibrillator discharges for people with VT that is mappable, that has this procedure, and I have some idea of this.

In that way, I think that we have the data, at least for this study, to make some decision, and I think it was as appropriately done as probably could have been done given all--

DR. SIMMONS: What is your point as far as Question 4 here? I don't see where you are going with Question 4.

DR. BRINKER: I don't think it would have helped to say that we should used as a control group data from the medical literature, and I don't think we should have used patients as their own control, which is defined as no recurrence of VT events in six months because we would have missed the boat, so the best we have is what we did have,

and that is at least a small group of patients randomized to drug therapy, and we do have also their own analysis of VT episodes before and after ablation.

So, I think that is the appropriate control for this study, and that is what they asked for, cooled ablation system, and the next study is not part of what we should be considering here.

DR. TRACY: It leaves the question open. There are different patient populations included within this study. There is the group that definitely got into it by having defibrillators and by having multiple drug failures, and then as things got relaxed as the protocol went on, there are a group of patients who get into the study for more compassionate use.

I think that more analysis is needed of the subgroups to really understand the safety of it. You know, we don't have enough information looking at total mortality on 6.3.2-29. I mean at least you look at that, and you say the mortality is highest in the compassionate use group. Maybe they didn't have defibrillators, I don't know, but that is the kind of analysis I think that has to come out of this.

But I think I more or less agree with what you are saying in terms of the best way to have set this thing, I guess it is probably the best way to have set this thing up,

but it would been I think better to have had longer with randomized to drug therapy, but, you know, have patients finally included with that. The majority of the patients were not randomized patients.

I guess I am happy with what I have to make a decision on here.

DR. SIMMONS: I think we should go on because you are starting to talk about things that we could have done or should have done. I guess the appropriate control that we would like to see is the patients randomized to drug therapy or patients acting as their own control with the number of VT episodes pre- and post-ablation as being one of the things to compare, which is the data they do have.

DR. VETROVEC: But that is also anticipating you know something different or expected something different out of the control group than you got, because the control group turns out to be very close to the medical literature. I mean it suggests that you know something that is not even in the literature or wasn't in this study.

DR. SIMMONS: What medical literature are you talking about?

DR. VETROVEC: The table right up there.

DR. BRINKER: In chronic success.

DR. SIMMONS: I still don't know where you are going with that. I mean the question is whether labeling

for this device, what do you want them to compare, the FDA has asked them to compare the device to as their own control. You can't have something that we don't have, so how do you want them to use their data in the labeling or in the pamphlet or whatever. Is that the question as I understand it?

You can't talk about anything else that could have happened, should have happened, or would have happened. So, how do you want it written up?

DR. BRINKER: I didn't take this to be specific, the labeling, since the labeling questions start with 7.

DR. SIMMONS: What is the intent of the FDA for this question?

DR. STUHLMULLER: Dr. Callahan, do you want to clarify what the intent of this question is, please?

DR. CALLAHAN: I believe in this case, what we are going to have to do essentially is get some effectiveness. Now, you have talked to that by putting in another gauge of effectiveness, that is the density aspect of it.

But I believe as the question was constructed, it was constructed if we are going to come down to judging effectiveness, how do we best do it since we have two or three different parameters to choose from.

DR. BRINKER: But this is not from a labeling point of view, is it?

DR. CALLAHAN: Well, it would be, yes.

DR. BRINKER: From the labeling point of view, I think the only thing you can do, it is simple if you just present the data, the data of the trial, and that is how effectiveness was--this is the data, this is what was seen, and one has to draw their conclusions from that.

DR. CALLAHAN: And you would include all of that as data?

DR. BRINKER: Not the past history or medical literature. I would include the data as they defined it, the criteria for acute and chronic success plus the data that they had analyzed that wasn't put in as part of an endpoint, and that is the VT density, and just let their data speak for itself as far as labeling.

DR. TRACY: I think VT density and actual success with the cooled tip ablation are the most important, that 61 percent or 60 percent, whatever that acute success was, and chronic success as indicated by lack of recurrence of any VT and perhaps lack of recurrence of clinical VT, if we can cull that data out of there, and VT density in terms of labeling. I think those would be to me the more important things to include.

DR. SIMMONS: Question 5. The following mortality results were obtained in the Cooled Ablation Study - total mortality, ablation treatment 16 percent, drug treatment 6

percent.

Does the following statement accurately reflect the mortality results of the clinical study? The mortality rate associated with the Cooled Ablation System may be higher for patients who receive cardiac ablation therapy than for patients who receive drug therapy.

DR. BRINKER: I think that Debbie made a good point arguing that they compared apples and oranges when you look at 16 percent and the 6 percent death rate because of the time delay. I think that one either expresses this in a proper time domain or simply says that during this study there was a 2 percent procedural mortality, and there is no evidence to suggest a long-term benefit in mortality, something like that.

But I don't think that one should say that it may be higher for people who get ablation therapy based on these numbers.

DR. TRACY: I think that is right. When all is said and done, you are comparing 150 patients to 14 patients, I think, if I am doing this right. I mean by the time you get out far enough, you have got 14 patients who are still in that control group, and it is sort or stacked against ablation in this way.

I think the acute complication rate is probably more appropriate, and nobody is saying you are going to fix

the cardiomyopathy or whatever it was that led to the high density VT in these patients in the first place, but I think there is still the fact that the acute morbidity/mortality of this is higher than it is for an SBT ablation, and I think that has to be stated, but I think you have got too few people in the control to really make much of this 16 percent versus 6 percent. It is there, but I don't think it is fair.

DR. BRINKER: It is the time domain more than the people because it is two years versus eight months, or whatever it was, four months, and they can express it to show no difference if you take similar mean times of follow-up.

DR. SIMMONS: Don't you think it is fair to say that the actual mortality rate associated is unknown, however, then compared in the time domain that there was no significant difference, but there is also no significant improvement in long-term mortality, something like that?

DR. BRINKER: Yes.

DR. SIMMONS: Specific Questions. Has the clinical study design of the Cooled Ablation System adequately demonstrated its use as a first line therapy for the treatment of VT, or should it be indicated for patients who have previously failed drug therapy?

DR. TRACY: No, one word answer, it has not.

DR. SIMMONS: It has not been proven as a first line therapy, we would all agree with that. Okay, so no, at least not in this patient population. There may be patient populations that it could be a first line therapy for, but those remain to be defined.

So, in this patient population with coronary disease, myocardial infarctions, cardiomyopathies, depressed left ventricular ejection fractions, this is not a first line therapy for VT.

Do we have to put in the labeling that the patients have to have previously failed drug therapy? I would say no.

DR. CRITTENDEN: You said no?

DR. SIMMONS: I would say no. I mean there are a lot of patients who have recurrent VT, that I just have very little faith in a lot of drugs. I think that should be a patient-physician sort of interaction. There are patients who have got contraindications, amiodarone, I mean I don't think you have to make it a patient have drug failure.

DR. VETROVEC: Well, failing drug therapy is inability to take a drug.

DR. BRINKER: It would be unusual for a person not to be exposed to a drug before they get this--

DR. SIMMONS: Very unusual.

DR. BRINKER: And if it was, then, you would have

to say that we have answered No. 6 in the opposite way that you answered it.

DR. SIMMONS: No, because I think the first line therapy for patients with recurrent VT is an ICD.

DR. VETROVEC: Well, that is preventive therapy, that is not primary therapy.

DR. BRINKER: Let's go back to this question, go back to 7. My feeling is that the labeling should reflect what this study showed, what this study studied, and I don't believe any patient in this study did not fail at least one drug therapy, is that correct? Were there patients who were not exposed to drugs?

DR. ECHT: I am not allowed to talk.

DR. BRINKER: Oh, she is not allowed to talk.

DR. SIMMONS: But there were patients in the study who did not get any drugs. There were very few, but there were some.

DR. BRINKER: All right. Well, if there were some in the study that didn't, and some of those patients were successfully treated, then, I don't think they need to be drug failures.

DR. SIMMONS: Wouldn't it be appropriate to say something like instead of saying, "The Cooled Ablation System is indicated for cardiac electrophysiology mapping, delivering diagnostic pacing stimuli and for radiofrequency

ablation of ventricular tachycardia attributable to ischemic heart disease or cardiomyopathy" period--

DR. BRINKER: Which can be mapped.

DR. SIMMONS: Well, I was going to say that next. The ventricular tachycardia arrhythmias should be of a cycle length or something--the next line I think should say, "Radiofrequency ablation of ventricular tachycardia arrhythmias in this patient population is not indicated as a first line therapy."

Is that good enough?

DR. TRACY: I think we have to be very careful. Realistically, the place that this thing seems to have had most of its use, I would think of it as an adjunct, an adjunct to drugs, an adjunct to defibrillator.

I don't know what percentage of patients ended up not having received any antiarrhythmic therapy, but I think it is a long stretch from this study to saying that this is a first line therapy for ventricular tachycardia. Regardless, you have the acute adverse events. Do we really want to say that this is a first line therapy for ventricular tachycardia?

I think that goes against other things that we know about VT management that make it seem that that should not be the first line therapy for VT. I mean we are not talking about RVOT VT.

DR. SIMMONS: Propose how you want to phrase it.

DR. TRACY: I would say yes in patients who have failed drug therapy and in patients whose VT is stable for mapping, and I would also throw in some other caveat statement, defibrillator or therapy should be strongly considered in this patient population as an adjunct or in addition to. I would add all those considerations into this indication. These are the people who were in there for the most part.

DR. VETROVEC: We are trying to really define clinical care for a whole population of patients rather than defining how this device is used. It seems to me that this device is used to improve the symptomatic problem of ventricular tachycardia, the clinical problem of ventricular tachycardia, and if that is deemed to be able to be done, and it's acceptable for the risk involved for a patient who has never been on a drug, that fits into what was done in this study.

On the other hand, the majority of people will probably already have been on drugs, which is what this study showed, but you are not defining what the doctor does. You are defining what the role of this catheter was or this system was in a certain population. That is a patient in whom clinically they would benefit from a reduction in ventricular arrhythmia frequency.

DR. BRINKER: I think the problem is in defining the patient population. My impression in reading this study was it was comprised mostly of patients who failed drug therapy or had been exposed to drug therapy.

DR. VETROVEC: There were very few people who weren't on some drug.

DR. BRINKER: And there were relatively few people, I think there was only a quarter of the people that didn't have an ICD. So, I think that somehow the background music of the indication should reflect that the study that validates this was performed in this group of patients.

DR. VETROVEC: These are patients who would clinically benefit from having a reduction in ventricular tachycardia arrhythmias.

DR. BRINKER: By this mechanism.

DR. VETROVEC: That is right, by this mechanism.

DR. BRINKER: Dan has previously used the kind of concept in setting the stage for labeling, the particular clinical study that was performed to qualify the device, and if you say that this device was proven safe and effective in decreasing the incidence of ventricular tachycardia in a group of patients, which were defined as follows by this study, then, I think you are helping.

You know, you said the majority of these patients had ischemic heart disease refractory to drug therapy and

had ICDs, and the benefit may not be restricted to this group, what was primarily proven in this group.

DR. SIMMONS: What about tacking on a sentence that says, "This therapy may be of benefit to patients as an adjunct to the management of symptomatic mappable ventricular tachycardia, and not as a first line therapy"? I think that leaves a lot of room for discretion, it is an adjunct to the management, and not meant as a first line therapy. I think we discussed the definition of the word adjunct at our last meeting.

DR. VETROVEC: Why not, if you are going to say it is an adjunct, just leave out, "and is not intended to be a first line therapy"?

DR. SIMMONS: I guess because I think it shouldn't be a first line therapy.

DR. VETROVEC: But you also point that some patients were treated in this way successfully albeit small without pre-existing drug therapy.

DR. SIMMONS: But it is small, and it is nothing compared to the larger studies that have been done on VT in other populations. It is just not big enough to make those kinds of claims.

DR. CRITTENDEN: Can we say may or may not be a first line therapy, or is that just too vague to make a difference?

DR. VETROVEC: If you are already defining it as adjunct therapy, then, I think that implies that you are not--

DR. SIMMONS: Why don't you like "not as a first line therapy"?

DR. VETROVEC: You are the one who is very unhappy with the number of patients that are involved in this, and the control groups, and now you are trying to make very sweeping definitions of how to use the device instead of allowing physicians to use some clinical discretion.

DR. TRACY: Somehow the word adjunct to therapy has to be there. We cannot say this is a substitute for ACE inhibitors, beta blockers, diuretics, we cannot this is a substitute for revascularization. There is a whole lot of first line therapy.

So, I think somehow having that statement "is an adjunct to the therapy of ventricular tachycardia," whether we add the phrase "not intended as a first line," but I think we can't say that you just ablate this and then they go away, then they are happy.

So, I would be content to say this is intended as an adjunct to the therapy--

DR. BRINKER: I think that the real issue here is to avoid very restrictive terminology that might put a physician who uses this in an appropriate patient as a first

line entity in some sort of medical-legal or reimbursement bind, and I don't think that should be our business.

I would agree with George, as well.

DR. SIMMONS: Let's go on then. No. 8. Is the proposed Contraindication section appropriate? Are there any other contraindications for the use of this device?

Contraindications: Do not use this device in patients with active systemic infection, who have a contraindication to heparin, with a mechanical prosthetic heart valve through which the catheter must pass, with left atrial or ventricular thrombus.

DR. BRINKER: I think that the heparin contraindication should be stricken, because of the embolization issue. One might put a warning that appropriate anticoagulation is--that there is a risk of systemic thromboembolism if appropriate anticoagulation is not obtained, but that could be done outside of heparin.

The other issue is that left atrial thrombus is only important if you go transseptally--what do you mean no?

DR. SIMMONS: Those catheters pop up in the left atrium without even wanting them to, I will tell you.

DR. BRINKER: But they don't go into the left atrial appendage or the septum very often. We do catheterizations all the time, and we pop retrograde in, but we use as a contraindication to TS atrial thrombus. I would

be happy saying that ventricular thrombus is a contraindication, but I wouldn't be happy making everybody do TEE to exclude atrial thrombus if you weren't going to do a TS to begin with.

DR. TRACY: The labeling for the Cordis Webster Diagnostic Catheter has the words, "via the transseptal approach in patients with left atrial thrombus from axonal or intra-atrial vascular patch."

DR. BRINKER: That is fine, if you want to differentiate.

DR. VETROVEC: Probably similar labeling would be appropriate.

DR. TRACY: There is also a section on Warnings that I think is appropriate that is for the standard catheter, is it assume that those warnings will also be included?

DR. VETROVEC: Yes, I think that is a fair assumption. In the other catheters you mean?

DR. TRACY: Right.

DR. VETROVEC: I would support Jeff's comment about the warning about adequate anticoagulation. I think that seems critical from the data, that the people they got in trouble with were people that maybe weren't well anticoagulated.

DR. SIMMONS: But the thing is you want to move

that from a contraindication, which is stronger, to a warning, which is less strong.

DR. BRINKER: The contraindications to heparin, you can get anticoagulation without heparin. There are a bunch, you know, liporhodin, there is a word, dan-something, I don't know, there are a couple of direct thrombin inhibitors and other things that are available that will give you anticoagulation, so I would just take away the contraindication.

DR. SIMMONS: I am happy with that. Just looking at this article from Kim and Howard Ruskin, the people they excluded included patients with--I mean is this in the Warning section, I haven't looked--patients with unstable angina, heart failure, aortic stenosis. They should be in the Warning section probably.

Shall we go on to the next question? No. 9. The Cooled Ablation RF Generator has impedance and temperature cutoff settings of 500 ohms and 110 degrees Centigrade. During the clinical study it was recommended that the RF Generator be used with temperature and impedance cutoff values of 200 ohms and 100 degrees Centigrade.

Is a caution statement which reflects the data collected during the clinical study appropriate or should the RF generator be modified to limit the impedance and temperature cutoff values to 200 ohms and 100 degrees

Centigrade?

An example of the caution statement is listed below. Clinical studies to evaluate impedance cutoff settings greater than 200 ohms and temperature cutoff settings greater than 100 degree Centigrade have not been conducted.

That is a tough one. I certainly would like to leave the investigator with as much play as they possibly can, but clearly if this was as heart valve, and there was no data collected on the heart valve on certain sizes, we have eliminated those sizes. There are other precedents for this kind of thing. If there is no data collected on those settings, should those settings be allowed outside some investigational study or should the commercial use of the device be limited to what was studied?

DR. BRINKER: In the caution, it just says that there is no data available. It doesn't restrict you, to use whatever you want.

DR. SIMMONS: That is what I am saying.

DR. BRINKER: I think this is okay.

DR. SIMMONS: You don't want them such they can't go above 200 and 110? That would be a very simple thing for them to do.

DR. BRINKER: I don't know how simple it is.

DR. SIMMONS: It would be very simple, very

simple. Does it matter? I mean it is a safety issue.

DR. TRACY: You have visions of somebody pulling out a great big ball of clot, you know, if the temperature was up to 550 degrees, pulling out a big blob.

DR. SIMMONS: If they have never tried it. I mean I guess we can't ask them if anybody has ever tried it.

DR. TRACY: It is not going to go above 50 watts. I think the maximum output is 50 watts. I think it is not likely that you are going to get a big ball on the end of the catheter, but I think that the reality is you probably won't see impedances of that high.

I mean given that this is a cooled tip catheter, you would have to have sort of solar heat within the myocardium if you got much above 100 degrees measured at the catheter tip. So, I am not sure that it is much of an issue.

DR. SIMMONS: I just don't know.

DR. TRACY: I just think it is a little bit difficult for people who don't know to know where to set the thing, and I think there should be a big label of something on the device that says these are the parameters at which this clinical study was done or this is the recommended range at which you should be doing things, you know, to have some kind of a very clear statement because chances are again nobody is going to pull out the packaging and look at

it and say where was I supposed to set that thing anyway.

So, I think it should be pretty obvious when the person looks at the device what it should be set at.

DR. SIMMONS: No. 10. Market approved RF ablation systems demonstrate a small difference between the displayed temperature measurement and the actual temperature measurement. However, due to the saline cooling feature of the Cooled Ablation System, there is a greater difference between the actual tissue temperature and the displayed temperature. If the operator misinterprets the temperature displayed on the RF generator, there is the potential for tissue temperature to exceed 100 degrees Centigrade. This could result in coagulum formation.

Which of the following alternatives minimizes the possibility for the operator to misinterpret the displayed temperature as the tissue temperature instead of the electrode temperature?

(a) Instead of displaying the recorded temperature on the front of the RF generator, display the change in temperature as an increase or a decrease and show the magnitude of this change. For example, increase or decrease a change of 1 degree, or (b) a caution in the labeling which reads: Caution - the displayed temperature is not the temperature of the tissue. It is the temperature of the cooled electrode only and does not represent tissue

temperature. And operator training that explains that the temperature display on the RF Generator is not tissue temperature but the temperature of the cooled tip electrode.

DR. TRACY: I have no clue what that top box means. If I saw something like that, it would mean nothing to me. I think that the caution, the display temperature is not the temperature of the tissue, that makes sense to me. Again, it is the kind of thing that it would be better to have it immediately visible to the operator.

DR. BRINKER: It should be on the device, right under the readout of the temperature, because there are going to be people who use this eventually, if not right away, who don't go through whatever training program that you have--yes, there will--and there will be also people who go through the training program half asleep or on the cellular phone. So, it had better be on the digital readout, right below it.

DR. SIMMONS: There is going to be first-year EP fellows in July.

Let me just see what the front of the box looks like. So, the temperature display on the front of the box just says temperature, it doesn't tell you whether it is tissue temperature or catheter temperature or any other kind of temperature. That doesn't seem very good.

DR. TRACY: I think that is why you do have to

have on there the displayed temperature is not the temperature of the tissue. I think that you have to state that.

DR. SIMMONS: I don't know how easy that will be to do, change the label, but I think that is something that should be really considered strongly, on the front of the box.

No. 11. Is the following individualization of Treatment section appropriate? Clinical studies have not been conducted to determine the mortality rate of patients who receive cardiac ablation therapy as an alternative to ICD implantation. Patients should not receive cardiac ablation therapy as a replacement for ICD implantation.

Well, I like this one, but since I have been outvoted every time it comes up, I don't know whether I want to go there again.

DR. VETROVEC: I think that is all right. I don't have any problem with that. It seems to me that that is not dictating what you are doing. It is just saying it is not proven to be a replacement for.

DR. SIMMONS: But it says patients should not receive ablation therapy as a replacement for ICD implantation.

DR. BRINKER: I think the critical issue here is that if you were going to, for whatever reason, put in an

ICD in that patient already, and that would probably most likely be for a very high-rate VT or an unstable VT, you should do it anyway.

I mean we already know that the recurrence rate and inducibility rate is very high. The issue here, I like this statement actually, because it prevents the misleading thought on some people that maybe if I had a rapid rate and this patient is unstable even at a lower rate, I can get away with just doing this as opposed to the patient who has a very well tolerated, relatively slow VT, but disturbing, and whom you wouldn't necessarily put an ICD in, they could get this without an ICD.

DR. TRACY: I like the essence of the statement, but I might just be a little bit more specific. It was never intended as a substitute for ICD therapy.

DR. BRINKER: That is a little editorializing.

DR. TRACY: Clinical studies have not been conducted to determine whether this is a substitute for a defibrillator therapy. I mean it is fine the way it is. Somehow the absence of this message has to get through. We have information that is pointing us in the right direction what to do with certain patient populations, who benefit fro defibrillator therapy.

I don't think that we have information from this study to say that ablation therapy is a substitute in those

patients. I think this is a weak way of stating it. It is okay, at least it gets something stated there. I would probably state it a little more directly this has not been compared to--this is not a study comparing this therapy to defibrillator therapy, but it is not know, it is not studied. This is okay, but I would word it more strongly, I think.

DR. VETROVEC: It seems strong to me, "patients should not receive cardiac ablation therapy as a replacement for ICD." It sounds strong to me.

DR. SIMMONS: No. 12. Is the proposed Patient Counseling Information appropriate? Are there any additional points you believe should be included?

I think you made some comments before about the pregnancy issue?

DR. TRACY: That is in the Warning section, the pregnancy. The Counseling section, I forget already.

DR. CRITTENDEN: Are we talking about it being a low risk?

DR. TRACY: I agree. The phraseology "low risk," I don't think it is fair to say that. Cooled catheter ablation may permanently cure your arrhythmia or may reduce the frequency of your arrhythmia occurrence would probably be a better way of stating that. And catheter ablation is a less invasive non-surgical option that uses a type of energy

called radiofrequency--it is less invasive than surgery, but it is not less invasive than medication.

I am not sure it is less invasive than defibrillator implant either, to be honest.

DR. SIMMONS: I think we have made our points over and over again on the risks and whatnot. When you make your proposal, you can just make the recommendation that the sponsor work with the FDA to change the patient counseling to more accurately demonstrate the risk and the lack of demonstrated effectiveness overall.

DR. VETROVEC: There is a statement in here that says, "Death from this procedure is very uncommon" on page 219. I guess I have a little bit of a problem with that statement. That is in the Patient Information. At least my definition of uncommon and the one from this study may be different.

DR. BRINKER: With that rate, you know, approximately 2 percent--

DR. SIMMONS: According to the literature, theirs is 4-something percent even after they culled it down and everything, theirs is 4-something percent.

DR. BRINKER: What I was going to say, the procedure is not a low-risk procedure, and I think to protect everyone, including the operator, in the future, people shouldn't be getting material that claims this is low

risk when the informed consent should tell them what the risk is, which should be 2 to 4 percent.

DR. SIMMONS: I guess these are supposed to be written in terms of eighth grade English or something like that, I guess including 8 percentiles or 4 percentiles may not be appropriate.

DR. TRACY: Probably procedure-related adverse events in patients randomized to ablation, death occurred in 1.3 percent. There was a major adverse event occurring in whatever percent. Is 1.3 percent very uncommon, is it uncommon death can occur? Death can occur with this procedure?

DR. SIMMONS: I think we actually need to move on and let the company and the FDA negotiate mild, moderate, if everybody agrees.

DR. VETROVEC: Uncommon would not be an appropriate term.

DR. SIMMONS: No. 13. Do you believe a Physician Training requirement should be included in the labeling?

DR. BRINKER: Yes.

DR. SIMMONS: Yes.

No. 14. Do you have any other suggestions for the labeling? Other comments?

DR. CRITTENDEN: Do we mandate echocardiography? Should this be stated?

DR. SIMMONS: I don't think so. They had had an echo done at some other institution, that you have got the results from. I don't think so.

DR. BRINKER: The echo, I guess is primarily for left ventricular problems. It should be done within some time frame before the procedure, but maybe somewhere in the part where it says, warnings or whatever, there is a risk of thromboembolism, and echocardiography should be done to exclude left ventricular--if a TS in mandated, that transesophageal cardiography should be done to rule out left atrium.

DR. SIMMONS: Where would we put that, in the Warning section?

DR. BRINKER: I don't know. These guys can figure it out.

DR. VETROVEC: Can I just ask you to look at patient selection and treatment? We don't have to work through it all, but--

DR. SIMMONS: What page are you on?

DR. VETROVEC: 2-8, 7.1 and 7.2. Somehow this doesn't fit what we have already suggested, first of all, about the heparin issue. I don't know, something about this section didn't read well to me in terms of it seems to me in a sense nonspecific. I don't know whether these are warnings. They are all kind of peculiar places that this is

put in here, it seems to me.

DR. BRINKER: But the FDA knows about our feelings about all these other things, and I am sure they can work out a better stylized version of this.

DR. TRACY: Are you suggesting that the issue of echocardiography be raised here?

DR. VETROVEC: Well, if there is really going to be a section on this issue special considerations in treatment, that might be what it would be called, then, you have got to deal with the anticoagulation issue if you don't want to make it a warning or make it a descriptor, you could list the areas where it has not been established, and list the issues regarding echocardiography. That is certainly a way you could go about it.

DR. SIMMONS: This actually seems like a good place for that, you know, have them discuss the heparin issues and also the echo issues. This can all be worked out later, I think. These are sort of technical issues, and we should move on.

Are we ready for 15? Do the data presented adequately demonstrate the safety and effectiveness of the device as labeled? The answer is no, so the question is how are we going to relabel it.

No. 16. Are there any other issues of safety or effectiveness not adequately covered in the labeling which

need to be addressed in further investigations before or after device approval?

I assume what they are talking about here, I am not sure what the intent of the FDA is here, are they asking post-market studies need to be done? Is perforation going to turn out to be 10 percent of all the patients? I mean should there be some tracking of this? I mean are the complications so out of line that we are really concerned about it? I am not sure about those answers frankly.

DR. STUHLMULLER: Dr. Callahan, do you want to clarify the intent of the question a little further, please?

DR. CALLAHAN: As you rephrase it, that is exactly what we are looking for, whether there are any post-marketing things that you consider tracking.

DR. VETROVEC: It would mostly be procedure related, I think, procedure related outcome.

DR. BRINKER: I guess what you are looking for is for further evidence of safety, I mean because it is still a relatively small cohort, and there is still a relatively high percentage of morbidity and mortality, and we don't have enough information to know whether the lesions are bigger, in fact, so much bigger that they cause a problem, and we don't have a comparison with off-label use of this valid, so I suppose some sort of post-market study to look at safety would be appropriate.

DR. TRACY: The other issue, there are two points of safety, I guess safety and effectiveness. There is the acute and then the long term. I don't know whose job it is to figure out what the long term is on that, but if you were talking about expanding this outside the realm of the initial intent of this population study, introducing it to other populations, will it lead to increased mortality by somewhat affecting what we now consider as first line therapy for ventricular tachycardia, whose job is it to know about that in three to five years?

DR. SIMMONS: I think those things are probably, you know, hospital practice committees, things like that. I don't think that is the province of the FDA to monitor off-label use of devices, is it?

DR. TRACY: You could argue that flecainide/encainide--I keep going back to that as a perfect example--that it took some kind of additional study to understand that that had serious mortality problems related to it. I am stuck.

DR. SIMMONS: I think it is new enough, it may be unfair that this is going to be the first company, that if we do approve it, that is going to be on the market selling this thing for VT, so even though there may have been other studies done, this is the first opportunity to really gather some long-term data, and I think it is probably fair to ask

them to do some acute and chronic mortality studies, complication studies.

DR. STUHLMULLER: I think to potentially put this into perspective, the issue would be, for example, if you were going to make a recommendation of approvable with conditions, would you establish as a condition for approval that they require for each new clinical site that they provide data on X number of patients, you know, at Y point in time regarding acute, procedural, safety, and would you, for example, require that the patients who are part of this PMA cohort be followed annually for X number of years to look for additional safety and efficacy data.

I think that is one of the ways you can look at the intent of what this question is.

DR. SIMMONS: That is what I was trying to get to also.

DR. BRINKER: I honestly don't feel that the long term issue, efficacy issue is an important one to me. The only issue I have, that I would want to do post-marketing surveillance on, a study on is get a bigger denominator to look at safety, because that data is still a little unsettled, and the procedural, that is the issue, the procedural morbidity and mortality, which is not small for this procedure, especially for this one, which albeit the data is all there as opposed to what is in the literature,

people can sort of cherry pick what they do, and write that up.

So, I think that we just need a cohort of a couple of hundred patients who get ablation to really look at what the procedural risk is.

DR. SIMMONS: The acute mortality, complications, and then a follow-up at three months on alive or dead thing, six months, a year?

DR. BRINKER: I am not that interested in long-term follow-up.

DR. SIMMONS: I am. I want to know what is going to happen to those lesions.

DR. AZIZ: One of the patients that had an autopsy had some sort of degeneration, whether that was there before the procedure or--

DR. BRINKER: Wasn't that the aortic valve replacement?

DR. SIMMONS: He was done right away, though.

DR. AZIZ: But the valve looked like it had some degeneration. Maybe that was older. I think there should be some surveillance, at least for three months. I mean in 10 years time, you don't want everybody doing it, but I think we should have something to tell us--

DR. TRACY: I think maybe that original cohort that is already in there, because there is a variety of

patients included in there in the different sections, to follow some percentage of those over time, three years, five years?

DR. BRINKER: The one issue that I would suggest, I would suggest that the company think about doing other studies that has nothing to do with the approval of the device, but the indications now to give us some insight as to the applicability of this device in subpopulations in which it might be a first line device or might expand what we are giving as indications now, so I would support that.

I would also support the company, if they found it in an altruistic kind of thought process, to do the study of cold ablation with the same catheter versus the no saline infusion, see what that showed.

Those are the kinds of things that would help all of you guys, as well as me as a referring physician, but those aren't the kind that we would mandate.

DR. VETROVEC: One of the critical issues is really the outcome in terms of complication, because I mean what is a little worrisome about this is the rate that occurred given that the people that were doing this were stars, and when you turn this loose in the world--so I think you have got to look somehow at acute complications.

DR. SIMMONS: I would like to draw the thing to a close unless somebody has some burning desire to speak.

We are going to close the open panel discussion. Would the company like to have a response?

DR. ECHT: Thanks. I am just going to sort of limit my response in the interests of time to one sort of main thing. I would really like the panel to think seriously about the indications statement and think seriously about whether the word "adjunct" and "first line" ought to be in there, the reason being, as you all know, I am an ICD advocate, but I also know the literature very well, and, for instance, ICD therapy is not first line therapy for hemodynamically stable VT. There has never been a study. The AVID was only done in patients with resuscitative cardiac arrest or hemodynamically unstable VT.

So, it is not fair, I would say, to stick that label here when you don't stick it, you know, on--you know, ICDs are also not, you know, what is a first line therapy then is the question. You can't say it is ICDs. To suggest that is, I think, not quite right. And using the word "adjunct" with the example that, for instance, ACE inhibitors are adjunct therapy for defibrillators, as well, again, the labeling for ICDs don't say that ICDs are adjunct therapy because these patients have ischemic heart disease, and they also need antianginal drugs.

It is sort of not, I don't think, fair to do that. I guess I would ask you to think about the statement the FDA

suggested in individualization of treatment, statement No. 11, or some modification thereof, and the description of the patient population that several panel members suggested, and then allow the physician to sort of make a judgment rather than sort of restricting it and calling it either not first line or not adjunctive, et cetera.

I guess that is my plea. Thank you.

DR. SIMMONS: Would the FDA like to jump in here?

DR. CALLAHAN: No.

DR. SIMMONS: There is no comments, we answered your questions?

DR. CALLAHAN: Yes.

Open Public Hearing

DR. STUHLMULLER: At this time, based on FDAMA, we need to reopen the public hearing. Is there anybody from the public that would like to get up and speak at this time? It would be specific to the discussion today.

[No response.]

DR. STUHLMULLER: No one? Okay.

Panel Discussion (Continued)

DR. STUHLMULLER: At this point, I will read the panel recommendation options for premarket approval approval applications.

The Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act require that the Food and Drug

Administration obtain a recommendation from an outside expert advisory panel on designated medical device premarket approval applications that are filed with the Agency.

The PMA must stand on its own merits and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

Safety is defined in the Act as reasonable assurance, based on valid scientific evidence that the probable benefits to health [under conditions of use] outweigh any probable risks.

Effectiveness is defined as reasonable assurance that, in a significant portion of the population, the use of the device for its intended uses and conditions of use [when labeled] will provide clinically significant results.

Your recommendation options for the vote are as follows:

Option 1. Approval - There are no conditions attached.

Option 2. Approvable with conditions - You may recommend that the PMA be found approvable subject to specific conditions, such as resolution of clearly identified deficiencies which have been cited by you or by FDA staff. Prior to voting, all of the conditions are discussed by the Panel and listed by the Panel chair.

You may specify what type of follow-up to the applicant's response to the conditions of your approvable recommendation you want, for example, FDA or Panel. Panel follow-up is usually done through homework assignments to the Primary Reviewers of the application or to other specified members of the Panel. A formal discussion of the application at a future Panel meeting is not usually held.

If you recommend post-approval requirements to be imposed as a condition of approval, then your recommendation should address the following points:

a. The purpose of the requirement.

b. The number of subjects to be evaluated; and

c. The reports that should be required to be submitted.

Option No. 3. Not approvable - Of the 5 reasons that the Act specifies for denial of approval, the following 3 reasons are applicable to Panel deliberations:

a. The data do not provide reasonable assurance that the device is safe under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

b. Reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended, or suggested in the labeling.

c. Based on a fair evaluation of all the material

facts and your discussions, you believe the proposed labeling to be false or misleading.

If you recommend that the application is not approvable for any of these stated reasons, then we ask that you identify the measures that you think are necessary for the application to be placed in an approvable form.

Option No. 4. Tabling - In rare circumstances the Panel may decide to table an application. Tabling an application does not give specific guidance from the Panel to FDA or the applicant, thereby creating ambiguity and delay in the progress of the application; therefore, we discourage tabling of an application. The Panel should consider a not-approvable or approvable-with-conditions recommendation that gives clearly described corrective steps.

If the Panel does vote to table a PMA, the Panel will be asked to describe which information is missing and what prevents an alternative recommendation.

Following the voting, the chair will ask each panel member to present a brief statement outlining the reasons for their vote.

DR. SIMMONS: I guess we are open for a motion.

DR. TRACY: I move that this device be approved with conditions. The specific conditions, notwithstanding comments from the company, would be that this device

indications listed as an adjunct in the treatment of ventricular tachycardia, and that the Patient Counseling section be reviewed by the sponsor and the FDA to make certain amendments including a closer look at the statements about low risk, death, and lesser invasiveness of this study, and that the Individualization of Treatment section be reviewed to discuss specific issues pertaining to echocardiography and heparin, and that some post-market surveillance be instituted following a certain portion of the initial cohort, and additional information on other patients treated with this device for acute adverse events, and the initial cohort for long-term adverse events and mortality.

DR. SIMMONS: Do we have a second for that nomination?

DR. VETROVEC: I will move.

DR. SIMMONS: We have a nomination and a second.

It has been proposed that the Chilli Cooled Catheter be approved with conditions, the conditions being that the Indications section be modified to include statements that this will be as an adjunct to therapy with VT with the patient population described above, changes in the Counseling section to make more clear the risks and benefits to the patient, Individualization of Therapy section will include descriptions of the requirement for

echo and anticoagulation, and the post-marketing surveillance study to be determined later, the number of patients in the initial cohort and the new patient population for risks and the complications associated with the procedure.

DR. CALLAHAN: Just a point of clarification, Patient Counseling is really one little section. You mean Patient Information section?

DR. SIMMONS: The Patient Information section. Thanks.

Now we get to vote.

DR. CRITTENDEN: I vote to approve with conditions.

DR. BRINKER: Approve.

DR. VETROVEC: Approve.

DR. AZIZ: Approve.

DR. SIMMONS: We are going to take a 15-minute break and then we will come back to look at Future Concerns section of the PMA.

[Recess.]

DR. SIMMONS: We are going to call the meeting to order.

DR. STUHLMULLER: There should be another handout at the table with a list of questions for the afternoon session. Megan Moynahan from the FDA is going to be leading

us here.

Clinical Study Design Issues for VT Ablation

MS. MOYNAHAN: Good afternoon. My name is Megan Moynahan. I am a biomedical engineer and a reviewer in the Pacing and Electrophysiology Devices Group.

[Slide.]

This afternoon I will be giving you a discussion of clinical study design issues for VT ablation.

[Slide.]

Based on discussions that we have had with the panel members and study designs that have been proposed to us by other sponsors, we have been developing two different study designs, a randomized study and a non-randomized study.

For this presentation, I will briefly describe each study design and ask for your input on some of the finer details in a series of discussion points. In addition, I will solicit general comments on each of the study designs at the end of each section.

The presentation will end with two general questions applicable to both study designs. The discussion points are based on questions that were included in Section 6 of your panel pack. Today, I have handed out a revised list of questions which are reordered to reflect this presentation. In addition, two new questions have been

added.

This afternoon's format is such that I will ask for your comments throughout my presentation.

[Slide.]

Let's begin with the randomized study.

[Slide.]

This study is designed so the patients are randomized to receive either ablation or drug therapy. The two groups will be compared in terms of long-term efficacy and complication rates in an attempt to show a comparable risk-benefit profile for the two treatment modalities.

[Slide.]

Along with the typical inclusion criteria for an ablation study, sponsors are encouraged to include the following. They should specify whether patients are required to have an ICD prior to enrollment in the study. They should specify the etiology of VT, for example, ischemic or idiopathic, in case there are differences in how those respond to treatment.

This is a randomized study with two treatment arms. Since patients should reasonably be expected to respond to either treatment arm, they should not be drug refractory or intolerant to antiarrhythmic medications.

[Slide.]

This raises the first discussion point. Question

No. 1 asks: Should inclusion be restricted to patients with a certain type of VT? How many symptomatic episodes does a patient need to experience to be included? How might patient selection criteria impact labeling indications, for example, should we restrict labeling to the indications studied?

DR. SIMMONS: Maybe we should back up and actually go back to your original proposal as the patients are randomized to either ablation or drug therapy, I mean before we discuss the relative merits.

Is that kind of a study a feasible study, you know, in 1998?

MS. MOYNAHAN: I know that the topic of randomizing--I guess when we are talking about a randomized study, what are the options for randomization. What I am proposing today is one possibility, and I think the rest of the presentation sort of assumes that we are randomizing to drugs. The idea is that other possibilities for randomization could also be proposed.

DR. TRACY: I think that was one of our, at least my major concerns with this packet we just reviewed, was who was the randomized control group, and I think if you were going to include multiple types of VTs, if you are going to include the idiopathic, LV VT, normal EF or you are going to include RVOT VT or something in a pretty much structurally

normal heart, then, comparison to drug is probably reasonable, but I think that depending on your inclusion criteria, it is going to determine whether or not you want to view the drug as being an appropriate comparison group.

I think if you are including the type of population that was included here or the initial intended population, which was a sicker patient population with ischemic VT or cardiomyopathy VT, that a comparison against now this device would be an appropriate comparison group rather than against drug, because presumably many of these people will have failed drug already, so I think who you include is going to determine what your control is going to be.

MS. MOYNAHAN: Yes, and I think it is valid that when we were making these recommendations, there wasn't a market approved system for VT ablation, so the thought of having another ablation system out there to randomize to wasn't an option.

I guess the third part of the question is how might selection criteria impact labeling indications, should the labeling be restricted, I think that still remains to be answered.

DR. TRACY: I agree with some of the comments that some of the experts on the panel made. There may be a type of VT where it would be first line therapy, but I think

there will be many more, the overwhelming majority of VTs that will not be a first line therapy.

DR. SIMMONS: I would just like to interject here that if there are members of the audience that would like to jump up and put their two cents' worth in, they are more than welcome at any time.

MS. MOYNAHAN: Shall I just move forward?

DR. SIMMONS: Yes.

[Slide.]

MS. MOYNAHAN: We have identified three outcome measures. The first is a measure of acute, procedural success, and would be applied to the ablation group only, assuming that drug therapy is the other arm, raising the next discussion point.

[Slide.]

Questions 2 and 3 ask: Is acute efficacy (procedural success) a clinically relevant endpoint for this study, and if so, how should it be defined? How should acute efficacy be assessed without a concurrent control group? What would be an appropriate historical control?

DR. SIMMONS: I think acute efficacy is something to keep track of, but it sure doesn't seem to have been much help in anything--I guess in some of the SVT studies, it has been good. It is really kind of a poor prognostic thing. I think your only hope is in some sort of a long-term success.

Like I said, it is good to keep track of it. It does help, but it shouldn't be a primary endpoint, I don't think.

DR. TRACY: I think acute efficacy in the more normal hearts, it is probably a reasonable thing, but here you are looking at acute efficacy of the mappable treated VT, at least in this study, that was the endpoint that we had, which doesn't predict clinical outcome in terms of how many episodes of VT the patient overall has because of these other VTs that these patients had.

So, again, you have to make a distinction between what you are treating. Some of the VTs do behave more like SVT, and acute efficacy is probably more predictive of clinical outcome than it was in this patient population, so depending on the inclusion criteria, it is going to determine what your endpoints of efficacy are.

MS. MOYNAHAN: So, it is safe to say we don't have to be constrained by how the definition was defined in a previous PMA discussion, are there different definitions for acute efficacy that we need to think about.

DR. SIMMONS: I think if you want to, say, this company came back and have an indication for RVOT tachycardia or outflow tract tachycardia of some nature, then an acute procedural success followed by some sort of long-term follow-up just for clinical recurrence might be

very appropriate, whereas, if you are actually looking at if another company wants to come and do another VT study with coronary artery disease, an acute procedural success is interesting and should have kept track, but shouldn't be kept as a primary endpoint.

Certainly, as far as what control groups you are going to look at, you know, there are some significant data on like RVOT tachycardia and what the success of ablation with that group is, I think you could use, can't you, couldn't you use those data even though they are off-label use?

MS. MOYNAHAN: As a comparison for the endpoint?

DR. SIMMONS: Yes.

MS. MOYNAHAN: Actually, we will be talking about where we would make that comparison, different possible control groups for that. Did you mean acutely or long-term follow-up?

DR. SIMMONS: You are talking about a historical control to compare, say, a new catheter tip.

MS. MOYNAHAN: Right, so that is kind of why we are asking whether it is clinically relevant, is it clinically relevant for the study, or does it give you-- Question 3 is asking once the sponsor presents that data to you, acute efficacy, how would you evaluate it, on what basis will you evaluate it.

DR. TRACY: Again, our problem today was the--pardon me--but the loose definition of drug control. There was not a standard way by which drug control was defined. It wasn't look at in a way that we could quantify it or understand what it means, and because there was such a mixture of patient populations within there, it was very hard to apply one thing to another.

So, if you were going to use a historical control of drug control, you have to understand exactly what you mean, is it EP rendered non-inducibility, what is it specifically that you are comparing to.

MS. MOYNAHAN: That is helpful.

[Slide.]

We have also identified two more outcome measures for this type of study. The first would be a measure of long-term success. This would be defined as either an absence of VT episodes throughout the follow-up period, in which case patients can be categorized as success or failure, and these relative proportions can be compared with two treatment groups, or alternatively, the number of VT episodes would be counted throughout the follow-up period, and the two groups could be compared that way.

Question 3, in terms of complication rate, we would consider all major procedure-related or drug-related complications in that calculation.

DR. TRACY: I like the idea of following the number of VT episodes. If you are dealing with an ischemic population and they have devices in place, you follow the number of VT episodes during the follow-up period. I think that is an important outcome point to follow. Yes, absence of VT is, of course, the most desirable outcome, but it is not realistic in a population that is going to have more than one VT present.

What you are trying to do is make life tolerable for these people in this type of situation, but then you cannot allow crossover from the control into the treatment arm, and we will be talking about that in a moment, because you just lose any comparison basis.

Then, to the more structurally normal hearts, RVOT kind of thing, I think is as a recurrence of the failure. I mean you would anticipate long-term success more in that patient population where there is an isolated focus that you are dealing with. So, any recurrence, I would think is a bad thing in that group of patients.

MS. MOYNAHAN: So it sounds like recurrence probably needs to be defined, as well, and it might be dependent on the indications that are being studied.

[Slide.]

This raised another discussion point, which is, what is an appropriate follow-up period to establish long-

term efficacy? What is an appropriate follow-up period to capture complication data? How long do these patients need to be followed?

DR. SIMMONS: It certainly looked like, in this study, that the first 90 days had most of the complications, or 90+ percent of the deaths in the acute complications. I was a little disturbed by the six-month time frame for an average. I thought a year was a more appropriate time frame for primary myocardial disease or coronary artery disease.

Probably patients with bundle-branch re-entry, vesicular tachycardias, outflow tract tachycardias, they have enough episodes that three- to six-month follow-up on those patients, they are going to recur if they are going to recur.

DR. TRACY: I think that is for the arrhythmia recurrences, that is probably reasonable. The only thing that Dr. Aziz was talking about, what about the aortic valve since you are crossing, at what point do we expect, if you have damaged them, at what point would you expect to see some problem related to that? Should you have a six-month echocardiogram follow-up or something like that when you know you have passed one of these large stiff catheters through the aortic valve?

I think you are not going to see significant valvular complications until probably later unless it is

something horrific, but there could be something pretty significant that you wouldn't know about for several months.

MS. MOYNAHAN: Okay.

[Slide.]

The next discussion point is Question No. 5. How should drug regimen changes be handled? For example, should the drug regimen be kept constant during the follow-up period (in both study arms), or can investigators work to optimize the drug regimen? When should medical management be optimized?

DR. TRACY: You have to do the right thing. If you have got somebody who has got a cardiomyopathy, you have to do the things that we know are good things to do. We have to treat them with ACE inhibitors, we have to treat them with beta blockers, we have to make sure they are not in failure, we have to make sure they are not having ischemic episodes. We have to do all of that even before we think about doing anything else.

That is a given, that they go under the best condition as is possible for that individual, but then to stick somebody with something--there may be something that you have to do to define, that you have made a change in a medical regimen. You may have to re-EP, or you may have to re-holter, you may have to re-something to attempt to keep them in that arm, if you are talking about using a drug

control arm.

You have to not say I don't care that you failed this clinically. You have to treat them differently, but you have to make a definition again of what you are doing, and probably subject it to the same initial definition that you used to determine that it was a successful effective treatment initially, whether that was by 48-hour holtering or whether it was by electrophysiologic study, but you have to have some kind of a definition, I would think.

DR. WILBER: Dave Wilber, University of Chicago.

This was a problem I think with this study, and it is a problem with a lot of studies. If you require that patients be drug refractory, then, the whole concept of how you should manage drug therapy doesn't make any sense.

I think that was the impossible thing we were asked to do in the study, is the vast majority of patients had failed several drugs, but yet we are still trying to find something else they should be put on.

I think the issues about drug therapy for VT ablation studies makes sense if, as one of the panel members actually proposed, a great study would be first episode of VT, compare them to a drug, compare them to ablation. The problem is when patients have already gone through several drugs, it starts to get very difficult to define new drug therapies and demand that they be non-inducible, and 40

percent of these patients were on amiodarone at the time that the study was introduced.

So, if the study is drug refractory patients, it just doesn't make sense to continue to compare them. I guess you can talk about optimized drug therapy or continued drug therapy, but if you do that, it is very hard to enroll patients.

In other words, if one of the conditions of the study is, okay, you have to fail amiodarone, so what we will do is we will randomize half the patients to get an ablation, and the other half continue amiodarone, you are going to have a very hard time enrolling patients because people want the prospect that something is going to be better, so you have to offer them a better alternative than the drug therapy.

So, one of the real problems with enrolling patients in this study was simply that who wanted the possibility of being randomized to a drug, and so it gets into the other issue that I know you are going to talk about, which is crossovers.

So, the only way in that kind of a study where you are asking a patient to be in a study where they have already got a very high chance of not--meaning regardless of what the facts are, the patient's perceptions are, well, I have already been through that route, and it hasn't done

anything.

They at least want an option that they don't have to be condemned to that route for six months or a year or two years. Although scientifically, they are appealing, I am not sure they are clinically reasonable studies to do, and I think it made it very hard.

So, I think the study that you are talking about might be different if you are talking about enrolling patients with their first episode of VT or whether they are relatively naive in terms of their exposure to prior drugs. That was a difficulty here, that may not be later, so I think how you answer this question really depends upon their prior history of drug exposure.

DR. SIMMONS: How about with patients like with bundle-branch reentry or an RVOT tachycardia that might actually respond to a calcium channel blocker? You might be able to do a drug arm in that group, and let them fail, and let them crossover, in which case you would probably want continued optimization of the drug all during the study, so if it took an increased dose or lesser dose, they couldn't tolerate the increased dose, and you have to decrease it. You do your best to keep them on the drug, and if they fail, they fail.

DR. WILBER: Once again, assuming a lot of people get there, it was the same difficulty as why haven't

randomized studies been done with drug therapy for SVT. It was the same problem, because most patients come to us because they failed drug therapy.

So, unless you go back and move this into initial therapy, so you can fairly compare two modes of therapy, I think that it is unreasonable to--and I think one should seriously consider alternative means, patients being their own control, or other things rather than the insistence on continued drug therapy, because, in general, ablation has usually been--or if somebody wants to get an indication for a primary therapy, so if the desire is to have an indication for ablation as the initial therapy for some, which I don't think there is an indication on the books for anything yet, that that is the case, then, it would make sense to spend a lot of time with drug therapy, but otherwise, a lot of these patients are already referred because they are drug refractory or don't tolerate or don't want, and these raise big issues about the representativeness of the patients that you enroll.

DR. TRACY: It depends, though, who ends up in the study is going to determine what the appropriate control is. We all know that we use medications as an adjunct to defibrillator care, to keep the number of episodes to a dull roar, so that it is tolerable for the patient.

In that case, to find something that is reasonable

is reasonable, and compare that to ablation in that population that is a heck of a lot sicker than somebody who is coming in, and you are considering using this as an alternative to drug therapy at all, and that is a whole lot different, and doesn't have a device at all, or does have a device versus somebody who has got a pretty normal heart.

I mean those comments are right, and I can see the difficulty in enrolling in this population, but still if somehow you are using drugs, it is probably important to maintain the same kind of a definition all the way through with that drug.

MS. MOYNAHAN: I just want to jump in and say for this study design, it is recommended that patients not be drug refractory because they need to be reasonably expected to respond to either arm of a randomized study, so no, they should not be drug refractory although I hear what you are saying about having a difficult time enrolling people who haven't already been on some kind of a drug regimen.

I think it is important to keep in mind that this is taking the idea of if a company wanted to do a randomized study where they were randomizing to a drug arm, how would we define that sort of optimum study, and we are kind of taking that train of thought and going with it today.

We will also be talking about a non-randomized version of the study where people act as their own control.

Let's move on to the next.

[Slide.]

In a randomized study, there is often an issue of whether a patient should be able to cross over to the other treatment arm. It is important to remember that this can be applied to patients in either arm of the study, so that rules need to be developed that can be applied equally in the decision to allow crossovers from either arm.

In addition, it is also important to not lose information about the safety or efficacy of the first treatment arm. Therefore, patients are typically restricted from crossing over to the other treatment arm until all the study endpoints are met for the first treatment arm.

[Slide.]

This raises the next discussion point. Question 6 has been summarized, but I will read it in its entirety.

Should patients be allowed to cross over from one treatment arm to the other? If so, do you agree that treatment crossovers could only be allowed once all the study endpoints have been met meaning if the long-term efficacy endpoint is defined as the absence of VT, crossovers could be allowed once the patient experiences a VT episode, and sufficient follow-up time is allotted to collect complication data?

Or if the long-term efficacy endpoint is a comparison of VT episodes between the ablation group and the drug group, crossovers could be allowed only if the agreed-upon follow-up period is completed?

Question No. 7 asks are there other circumstances that would allow crossovers?

DR. TRACY: To me, that was the biggest problem here. There is no turning back once you have done an ablation. You cannot undo it. So many people in the ablation group had a recurrence of some type of VT or another, but as soon as somebody in the drug treatment group had a recurrence of VT, and you don't know whether they would have 14 more that month, or 1,000 more that month, or that was the only one for the next 13 years, they were offered to go over into the other group.

So, you don't get any information that way at all. You can't use number of VTs, you can't use long-term mortality, you can't use anything from that information.

MS. MOYNAHAN: And that was because their definition of recurrence was any VT.

DR. TRACY: Any VT.

MS. MOYNAHAN: And it wasn't designed to answer the question how many VT episodes in follow-up compared to like a baseline.

DR. TRACY: Yes, and in this population, we are

not making these people healthy. We are providing a tolerable lifestyle for them. It is not like those that had defibrillators had no recurrent VTs after ablation, they did, and they did have recurrent shocks.

I think the definition of any recurrent VTs is where this thing got into trouble in the first place, with that control group, but I know somebody is going to pop up and say this is being applied to a different population, well, yes, but if you are talking about kind of population, you have got to agree that unless there is some overwhelming clinical reason why you have to take a patient out of that control, as defined by completely refractory VT incessantly occurring despite all attempts at optimization with medical therapy, then, you can allow them to cross over.

Otherwise, I think you do have to work to get it to optimal therapy. We have all seen patients like this who go into VT storms, you throw a little beta blocker at them for a month, and they are fine. They go away not having any more VT.

MS. MOYNAHAN: So, to satisfy your concern, you are saying that crossover could only be allowed if the follow-up is complete?

DR. TRACY: Yes, or you made a definition ahead of time that said this is the circumstances where I am not going to insist they go the full six months.

DR. WHARTON: Marcus Wharton, Duke University.

We were talking about this issue with regard to the Cardiac Pathways trial, and the initial protocol design, if you notice, is actually that there was a fixed period of follow-up if you were randomized to medical therapy, and that was changed early on to allow earlier crossover, and part of the reason for that was purely an issue of enrollment.

That is, if a patient is referred to you with medical refractory VT for this patient population group, and comes with the expectation of probably being ablated, and is willing not to randomize to medical therapy, and then gets two or three more shocks, they are not going to be real pleased with the concept of waiting six months, so they can finish out some arbitrary protocol, so it actually hampers enrollment for this type of designed trial.

You can think of designed trials in terms of how pure you want it to be, in terms of addressing scientific questions, but there is also the practical side that you have to be able to enroll patients, and it has to be at least semi-appealing to what patients want you to be doing with them.

DR. TRACY: But now you are in a good position to say even if I ablate you, you are going to have three or four more shocks. I mean you are in a good position to know

now that ablating them--and whoever does the next study can say we are going to randomize you between X and Y, and with X we don't know, and with Y we don't know, but we do know that long-term follow-up in both of these groups, it is very, very likely that you will have some form of recurrence. I mean you now know that.

DR. WHARTON: But you know that if you have one recurrence, too, but you don't know the density of the recurrence. I am in some ways just echoing what you are saying there. You can't have a flat clause that says the next six months you have no hope of ever being ablated, because you are going to get into situations where you are going to have to, so you have to maybe specify that prospectively.

DR. SIMMONS: How would you define when they can cross over? How would you determine when they can cross over?

DR. WHARTON: A couple of recurrences. You can either have a density, two recurrences in a month. It is arbitrary how rapidly you allow them to have recurrences.

MS. MOYNAHAN: It sounds like when you do it that way, you are classifying patients as either successes or failures as opposed to this randomized study design where you are going to be comparing the number of episodes in the two treatment arms, and that is a different statistical

analysis.

DR. TRACY: Could you use density, in a way introduce the VT density for that individual?

MS. MOYNAHAN: Not for an individual, but you could maybe come up with definitions of successes or failures that had to do with a certain density, yes.

Probably the reason why I raised Question 7 about there being other circumstances is that I was envisioning a situation where somebody might have been assigned to the drug treatment arm, and maybe it is doing a good job of keeping them from having another VT episode, but maybe they have intolerable side effects, would that be a reason to allow them to cross over, and then what would you consider that person, a success or a failure, how would you do that, or should that definition be changed for the drug arm to allow that.

DR. SIMMONS: If you can't take the drug, it's a drug failure. If you can't tolerate the drug or have side effects to the medication, it's a drug failure I would say.

[Slide.]

MS. MOYNAHAN: Before I move on to the non-randomized study, I will take any comments that you have on the randomized study.

DR. SIMMONS: I guess based upon the discussions we have had here all day, I guess I am much less

enthusiastic of a randomized trial. I think it is going to be difficult. I think the drugs that we use, especially in coronary artery disease, like amnio, have such long half-lives, trying to figure out whether the drug is working or not, or how it is affecting the patient today as opposed to a month ago, combination effects, I am much less enthusiastic I think today, now, than I might have been earlier today after thrashing through all of this.

My enthusiasm for a randomized trial based upon a drug is very low at this time for anything.

DR. TRACY: How about compared to a new ablation catheter or device compared to one that is now approved?

DR. SIMMONS: We have had these discussions before back in the defibrillator days. We can't really ask one company to buy another company's defibrillator and compare. You have to look at the cohort of data that is available in the historical literature. Unfortunately, this cohort of data that is available in the literature, I don't think is the standard that you want to hold somebody to. It has got a lot of problems.

I mean I think you would want maybe--I would like to compare it to off-label, just a meta-analysis of a large group of off-label stuff that had been done before as opposed to one company's attempt to do a study.

I mean can you randomize one device against a

device that has already been approved?

DR. STUHLMULLER: Dr. Callahan, do you want to address that issue or does anybody else from FDA, as well?

DR. CALLAHAN: That is the question, can you randomize against an approved device. That is really what the question is.

DR. STUHLMULLER: As a medical officer and one of the reviewers in a variety of device areas, we have a variety of devices that are randomized to another device, and it is an equivalence type study at that point, with a methodology that is set up to evaluate equivalence.

DR. SIMMONS: You would randomize like one stent to another company's stent for a coronary angio procedure.

DR. STUHLMULLER: That would be a fair example, yes.

DR. SIMMONS: You have done that? I have just never seen that done. I have always seen one compared to a historical base, a CPC kind of thing. I just have never seen a company propose I am going to randomize my stent to the--

DR. STUHLMULLER: In terms of data that is in the public sector, I mean there are studies that have been done. It's an equivalent study from one stent to another, and that is the way it is done where it is randomized that way.

DR. TRACY: It would have been--and I am

suggesting it to one of the investigators who is still holding onto this device--it would have been nice to randomize between--this company could have done their own device with the saline turned on versus their own device with the saline turned off, or doesn't it work that way? I don't know. Could you not deliver without turning saline on this device?

I don't know whether that physically is impossible, but it would have been interesting, and I don't know if future devices will have that possibility built within the device to use itself as a control.

DR. STEVENSON: I agree with you that would be a very interesting hypothesis to test, whether or not the cooling really makes a difference, and there was some enthusiasm for testing that hypothesis, but it was discouraged at the time that that was brought up.

Some of that I think also had to do with the issues involved of possible off-label use of a standard ablation catheter that was not cooled versus comparing it to the cooled RF catheter.

DR. CALLAHAN: One of our problems is trying to--I mean we are constricted by the law to say we need to be looking at things, for example, we can't compare one investigational device versus another--what would have happened in that case if you had each of their device,

whether it would be cooled or not cooled, would be an investigational, so from our point of view of the law, we don't have a legal comparison.

DR. TRACY: You don't necessarily know that bigger is better here. You don't know that, and you don't know when you are getting too big of a lesion, and in the RV outflow tract, why on earth do you need a 4-foot wide lesion. You just don't know. I don't know how to get around that problem. I can see, I guess it would have been off-label for this device to use it without the saline turned on, so you are really in a bind in that circumstance.

DR. SIMMONS: I am not so sure what the problem would have been, the comparison, you wouldn't have had a control then that you would have accepted.

DR. STUHLMULLER: I am not sure you can say, as Dr. Tracy referred to it, as off-label. I mean part of the issue is, is when you do a study, what do you want to end up with as an indication for use, and you need to use the device in the clinical study in the way you anticipate it being used clinically, so if you are going to do it with saline, then, you have got to do the clinical study that way. If you are going to use it as a standard catheter, then, that is how you try to set your study up, so you end up with data that supports what you want for your indication.

DR. TRACY: Suppose there is another device that comes through that has the same potential to be used either as a standard or as a standard plus something catheter. It would make sense to me to use it within that thing as a standard versus a standard plus something, and compare that.

MS. MOYNAHAN: Maybe I am going out on a limb here, but I think if there are marketed devices, and if have a new device that you are studying, looks just like the marketed devices, but it has this extra feature, that maybe you could compare it to itself. It might be possible to compare it to itself since the baseline--I think the difficulty that this company had is that they were going to be the first company on the market with a device like this.

DR. ECHT: But you can close off the saline lumens. In fact, in another limited study where we have mapping array, we have been able to use that, so, for instance, another company, should this catheter get approved, this could be a control for it. Just an idea.

MR. DAWSON: Hi. I am John Dawson. I am an FDA statistician. I have a question for the advisory panel and also for the panel clinicians who are here today. I would like to know whether proportional randomization, such as the 3 to 1 that was used in the Chilli study, facilitates enrolling control patients when the control arm is disfavored, and if not, I am wondering what kind of patients

we actually end up with in the control arm. Does anybody have any thoughts about that?

DR. TRACY: If you do it 3 to 1, but you keep your control really as a control, and you make every effort to keep them in that control, then, probably yes, it would facilitate entry into the study, but if you allow sort of willy-nilly crossover, then, you are no farther ahead to have them just maybe go in and do whatever they want anyway.

If you keep within a definition by what criteria you cross over, then, 3 to 1 I think would facilitate enrollment in the study.

MR. DAWSON: How about at the enrollment stage itself as far as patient willingness to be randomized is concerned?

DR. TRACY: It is not going to make any difference. It is your job as an investigator to say I am inviting you to be in this study, by the way, you have to a 3 to 1, you can't say that, parenthetically speaking, you have got a 3 to 1 chance. You have to present it straight up we are studying the effectiveness and safety of this treatment versus that treatment.

You have to present it that way. Just in terms of gathering information, I think it facilitates your ability to gather information, so maybe that is a better way of putting it. It is going to facilitate your ability to

gather information, but still for having information worth dealing with, you have to maintain the integrity of the groups, I think.

MR. DAWSON: Let me add, then, a third question. That is, is there any benefit in proportional randomization, and if so, what, from your point of view as clinicians?

DR. STEVENSON: I can just comment on our experience with proportional randomization in the trial that was presented today, which was that patients that were largely referred for possible entry into the trial came with the perception that their drugs were not working, and that ablation offered them a reasonable option for improving their quality of life.

As the drug treatment option was not very good, the fact that they were more likely to be randomized to receive the active intervention was an important factor in improving I think the patient recruitment after an early phase of the trial.

I think that would not be an issue where you have two potential therapies that are perceived as being a bit more equal than what we were confronted with in trying to enroll patients into this trial.

MR. DAWSON: Did you find you had to talk about the odds of being randomization to ablation?

DR. STEVENSON: Yes, we did, we did with this.

That wouldn't be the case if it was two more equal trials, but we had patients specifically referred for ablation, and the approach that we had to take was to say, well, we would like to enter you into this trial, we think this device may offer some improvement to you, but it's a randomized trial, you could wind up continuing on an antiarrhythmic drug, and we had some referring physicians and some patients who said no, I sent him there to get ablated.

MR. DAWSON: Thank you.

MS. MOYNAHAN: Are there any more comments on the randomized study?

DR. TRACY: I think that is because of the entrance criteria and the definition of success. That is where that study got kind of pushed to that point. So, in the future, I think we have learned something about if we want to get enough people--

MS. MOYNAHAN: You would be offering them two arms that are a little bit more equal, and then you would have definitions of success that might allow an earlier crossover or allow us to collect all the information that we need about them before they cross over?

DR. STEVENSON: I would just echo that with present antiarrhythmic drug options, it is just very hard to do this kind of a study in people that have already failed an antiarrhythmic drug, and I think you would have a much

better chance taking patients now that there will hopefully be an improved system for VT ablation, I think you would have a much better chance of taking people that have had a spontaneous episode of VT and randomizing those, so that you get a less refractory bunch.

Then, with the crossover issue, I think one of the other things that I think maybe we got an insight in today is mortality endpoint is not going to be meaningful in this kind of a trial other than it is important to show that it doesn't increase mortality.

So that to then have well-defined VT reduction endpoints, and then once that patient meets that endpoint and potentially crosses over, the follow-up is continued with an intention-to-treat analysis to be certain that mortality isn't increased by that therapeutic strategy.

So, you are really testing more of the therapeutic strategy, going to ablation early versus continuing with some other intervention, a drug trial maybe within a later ablation if that fails. This is clinically what practice really is.

DR. TRACY: Less sick populations like the other types of ETs, the 3 to 1 might really facilitate your reaching an understanding of efficacy, and I think it would be helpful from that standpoint.

DR. WILBER: Just to reemphasize, there are just

times when randomization to drug is inappropriate, and I think frankly the reason the study got off is I think randomization to drugs was inappropriate here, and it probably would have been better to have done something else, but that is what was required at the time.

Hopefully, one of the things that is going to come of this meeting is that there are times when that is simply inappropriate to do, and it is inappropriate to request in certain patient populations, when they are already drug refractory, to expect them to take drug therapy again, and hopefully, that is a concept that we can get rid of.

MS. MOYNAHAN: This is probably a good segue.

DR. STUHLMULLER: Can I ask one question with the issue of proportional randomization, I mean what I took way was that the issue of whether the 1 to 1 or proportional in part depends on what the perception is of clinical equipoise and that the more uncertainty there is regarding the clinical equipoise that it is more appropriate to go 1 to 1.

DR. WILBER: I think the other advantage that hasn't been mentioned here is that if you have a new therapy, we have thousands of patients described in the medical literature on drug therapy for which the recurrence rate is between 60 and 80 percent.

We don't need another thousand patients to maybe perhaps demonstrate that again, so one of the things about

proportional randomization is to have a new therapy that you want to learn safety and efficacy is that with a smaller patient population you can get more safety and efficacy in the new treatment arm as opposed to the treatment that has been around for a long time.

DR. TRACY: If you are comparing standard versus standard plus X, 50-50 is fine.

DR. STUHLMULLER: In more general terms, regardless of whether it's drugs, I mean whether there is clinical equipoise regarding the control arm versus the intervention, that that is the issue that you were trying to get at.

MS. HOFFMAN: Julie Hoffman, Medtronic CardioRhythm. I would like to revisit the topic of using this approved catheter to compare for future catheters, how do the conditions of your approval impact on a company moving forward to do those clinical trials given what you sort of defined your needs were for your conditional approval?

DR. STUHLMULLER: I think that is really question for the agency. I think it should get directed to Dr. Callahan rather than the panel members.

MS. HOFFMAN: May I do that.

DR. CALLAHAN: Do you want to repeat that question?

MS. HOFFMAN: I wanted to revisit the topic of using an approved ablation catheter to compare it for those companies coming forward with other catheters, and there were conditions for approval with this device, if, in fact, it is approved. I was wondering how those conditions impact on one's ability to go forward with that type of study.

DR. CALLAHAN: If I understand your question, you mean whether or not it could be used as an appropriate control in the interim while that data was still being collected?

MS. HOFFMAN: Yes.

DR. CALLAHAN: The conditions of approval mean that approval is granted, and then the conditions have to be met. It is still an approved device once it is approved, so it would be a legitimate control. The labeling might get affected by the results of the follow-up, but if company A wanted to use company B as a control, once it is approved, that is an approved device, and they wouldn't need to wait until the complete study is done.

MS. HOFFMAN: So, one wouldn't have to wait for any of the other findings from what you asked as a condition because it may impact on some other aspect of their labeling or whatever in the future in order to use it as a control.

DR. CALLAHAN: Right. The conditions as they were voiced today, there were two types of conditions. One was

conditions that we actually interacted with the company and changed the labeling, and made the labeling reflect what the panel had suggested.

The other types of conditions, if you will, were more follow-up conditions, and those wouldn't have to be met before it could be used as a control.

MS. HOFFMAN: Could one use, however, their device and their, I guess data that is available as the historical control rather than doing a prospective trial since it seems that historical data is often referred to, and actually was referred to their submission?

DR. CALLAHAN: The problem with that as a historical control is that you don't have their data. We have their data, but you don't have their data, and even when they publish their data, the question arises with us, as it did in the MADIT study, for example, that we have the data. The data did get published in the literature, but there wasn't enough in there to address a lot of the crossovers that were present in that study, as well. So, that gets a little dicey for us. We can use historical controls, but the reality of something like this is you probably will not have their data.

MS. HOFFMAN: I realize I won't have their data. Thank you.

MS. MOYNAHAN: Let's move on to the next slide.

[Slide.]

The non-randomized study is designed as a single-arm study where each patient acts as his or her own control. The idea would be to count the number of VT episodes during a baseline period, apply RF ablation, and then count the number of VT episodes during the follow-up period and compare.

[Slide.]

Raising the next discussion point, Question No. 8. What is an appropriate baseline period of counting VT episodes? Under what circumstances could the baseline data be obtained retrospectively? What factors contribute to the duration of the baseline period?

DR. SIMMONS: With the devices that are being implanted today, I guess if you are really talking about patient with an ICD implanted, you could actually do retrospectively back months and actually collect lots of retrospective data that would actually be pretty accurate.

If they don't have ICDs, then, you are probably looking to having to follow somebody for at least--well, it depends on how many episodes they are having unfortunately. I mean if they are having one episode a month, you might have to follow them six months in order to actually collect any accurate data. I mean if they are having lots of episodes where they have got a relatively high density of VT

events, a month might be fine.

I think it is a difficult question to answer. I am having trouble putting an exact number on the number of months that you have to follow somebody.

MS. MOYNAHAN: It sounds like what you are saying is it depends on the density of the episodes, and that we might have a different criteria for high density versus low, and maybe those two terms could be defined.

DR. SIMMONS: Yes.

DR. TRACY: If somebody wants to think about doing an ablation on somebody who is having one episode of VT a month, is that necessarily the right thing to do given the adverse events associated acutely with the performance of the procedure, particularly if the VT is something that is pace terminable or something that is a tolerable thing, that is probably not an issue--it's not the place you want to go now necessarily.

It is certainly easier, I think, to define in a higher density group of people, I think easier to define for two months or if six episodes in one month, 18 episodes in two months, something like that versus the two-months after, so density makes a difference, but you are asking a whole different question about doing an ablation on somebody who has such a low frequency of VT in the first place, is it really a reasonable thing to do.

MS. MOYNAHAN: Are you saying that there should be a minimum density to be enrolled? Actually, that is another question that is going to be coming up shortly, but I will ask you now.

DR. TRACY: I don't know. If I was 27 and I wanted to get pregnant, and I had RV outflow tract VT, and I didn't want to take calcium channel blockers or beta blockers, I would want an ablation. I might only have had one big long episode of that, but I wouldn't want to take drugs.

MS. MOYNAHAN: For the purpose of this kind of study, though, I understand what you are saying, but for the purpose of designing a study around that, would it be possible to identify a minimum density of episodes?

DR. TRACY: From the data that is submitted here, there is an enormous--I mean the pluses and minuses are huge, so I would think that you could, but there is going to be a tremendous amount, even within an individual, there is going to be a huge variability, and it is going to be difficult, I think, to state exactly--I don't know how you would come up with the exact number that is the right number to use.

I mean if somebody goes through one of these kinds of storms that some people get into, they may have like 10 episodes, but if you can sort of, what we have done in the

past would be to kind of ride it out, and the chances are they might be fine.

So, I feel you need a period of time, like a couple of months, assuming that you can get there, and use some time frame rather than thinking that I am catching somebody in an acute exacerbation of their arrhythmia.

MS. MOYNAHAN: I understand what you are saying.

DR. SIMMONS: I think with a non-randomized study, the patient population is going to be larger. I mean your available population to look at is going to be larger. I think that may help offset the variability a little bit. I mean you ought to be able to get a lot people into a non-randomized study, and therefore, if you put some definitions on the number of VT episodes, a low number for so many more months, and you can decide on a number like that, and then you could actually follow them for a longer period of time, too. But that may help take away some of the variability, but I think with the non-randomized study, you are going to have a lot more patients enroll.

MS. MOYNAHAN: For the non-randomized study, I guess the idea is you need to be able measure change in an individual.

DR. SIMMONS: But there is going to be so much variability, you need more patients to make is significant.

MS. MOYNAHAN: But each person acts as their own

control.

DR. SIMMONS: Intrapatient is so variable. I mean you might have one patient who had 10 episodes this month, but then the month before he may have had none.

MS. MOYNAHAN: I see what you are saying.

So, if you can't retrospectively count episodes, I guess the question I am throwing back at you is what period of time is an appropriate time to start counting them to get a feel for the patient?

DR. TRACY: Two months or three months. You are usually seeing defibrillator patients every three months to do impedance checks or whatever.

MS. MOYNAHAN: But these would be patients who wouldn't necessarily have that, they are the ones that you can't retrospectively interrogate and count episodes. They are being enrolled and then they are going through a baseline period, so that you can start counting.

DR. TRACY: So, are you saying that you are going to put in defibrillator, so that they can get into the study?

MS. MOYNAHAN: That is a later question.

DR. TRACY: It's a different population. People who need defibrillators are different from people who have episodes of clinically tolerable, repetitive episodes of VT. You are putting in a defibrillator because you think that

there is somebody at risk for sudden death.

So, that milieux is different from somebody who is a walking VT. I don't think that those are comparable at all. The easiest group to work with using the patient as their own control is going to be the defibrillator population who you can look and see how many episodes they had since your last check, you know, this last three-month check, do your intervention, see them in three months, and make that comparison.

That is a lot different population.

DR. SIMMONS: Think of an RVOT tachycardia. You might actually treat that patient completely differently. You might not put him in this kind of a study. You might do an induction study, and just like we said, that is more like an SVOT, where a post-procedure study is going to be very predictive, and you can follow them just prospectively without drugs. So, that is a completely different group.

Again, you have to define what population you are talking about.

MS. MOYNAHAN: So, it sounds like it also might be impacted by your inclusion criteria for the study?

DR. TRACY: Definitely, yes.

MR. DAWSON: I was just wondering, Dr. Simmons, if you could explain a little bit about your reasoning in saying that with the non-randomized study, you might have a

better enrollment or an easier enrollment.

Is that assuming that if there is randomization, it would be randomization against drug treatment or in general? Do you consider non-randomized studies easier?

DR. SIMMONS: I guess I must by a cynic, but I suspect to a large extent that the number of patients who are going to be available is going to depend on the enthusiasm of the investigator, and you are going to have, I think, a relatively low level of enthusiasm even among the most motivated investigator to randomize a patient against a drug. The faith of most clinicians in the available drugs today is low as far as preventing VT or not having significant side effects, and whatnot.

I think, number one, it is going to be in the level of enthusiasm of the investigator.

MR. DAWSON: What about the leverage associated, the period of time after which a patient randomized to control could be converted to the experimental treatment, that is, if a patient is randomized to drugs, and they have to wait one month or three months or six months before they are eligible, does that make a difference?

DR. SIMMONS: That would make a big difference.

MR. DAWSON: Any idea what that length of time would be?

DR. SIMMONS: I think for most patients, a month

is something they could live with. I think three months is somebody who is having current shocks or episodes of VT, that is not something they are not going to be very comfortable with. I think you might get most patients through a month if you are an enthusiastic investigator and willing to sit and go over things.

MR. DAWSON: So that enthusiasm level is very important.

DR. SIMMONS: I think it is the single most important thing getting a patient in the study is your level of interest in finding the answer and being a scientist, and getting them in the study.

MR. DAWSON: Thanks.

DR. STUHLMULLER: There were a couple of comments made about sample sizes relative to randomized versus non-randomized studies. Do you want to respond to that?

MR. DAWSON: You mean with respect to the total sample size?

DR. STUHLMULLER: Yes.

MR. DAWSON: The impact is not necessarily all that great as the 3 to 1 randomization, it is not necessarily that much greater than a 1 to 1, because it tends to even out. It can be adjusted and you end up making choices among study parameters, such as the power that you want to have, and also the endpoints. Some endpoints will

do better with proportional randomization than others.

It is not a simple straightforward rule that I know of to say that you should or should not do proportional randomization because of the impact on measurement problems or entrance problems.

DR. STEVENSON: Before you leave, sir, I know somebody at Duke did a study looking at the frequency of supraventricular arrhythmias, trying to quantify the changes more by looking at the interval between episodes as opposed to the absolute number of episodes in a fixed period of time.

Would that be something that is easier to handle if you defined the median time between episodes over a given period of time, and then showed that there was no episode over a subsequent follow-up period?

MR. DAWSON: I would expect so simply because you are talking about a continuous variable versus some kind of a truncated or quantum response. So, the more information that you are able to use, typically, the more power you can get, and the amount of time measured exactly probably would be more help as far as the sample size is concerned.

DR. STEVENSON: So, an increasing interval between episodes as opposed to just simply a fixed reduction in the number of episodes. I would think that for the crossover, rather than specifying an absolute time, you might want to

have at least built in there a certain frequency of events, so if somebody really has a storm and it is only Week 2, they are either going to drop out of the study or you might as well cross them over and follow them, I would guess.

MS. MOYNAHAN: I would like to ask a follow-up question for this slide. I know that having a baseline period is something that is difficult for patients being enrolled in a study and also sponsors who are carrying out the study, but we have talked about how you will need a baseline period if there is not a retrospective method for counting VT episodes.

So, I am wondering should an ICD be required for patients in this kind of study, or if a sponsor is not amenable to having a baseline period, or is there some other retrospective way of documenting VT episodes that has some accuracy and reliability?

DR. TRACY: You can't answer that without saying that it depends on the clinical scenario, what kind of patient you are studying.

MS. MOYNAHAN: I guess in this type of study design, when patients are acting as their own control, you need to be able to measure a difference after the ablation period, so you need to have counted the episodes before and then compared it to the count afterwards.

DR. TRACY: I think if you are using patients as

their own control, you can't have the people who are less sick. You pretty much can't. I wouldn't think you could do it that way with them.

DR. SIMMONS: Again, if you are talking about a life-threatening arrhythmia, and a patient has a life-threatening arrhythmia, then, they are going to get an ICD implanted, and you are not going to enroll them in the study at that point in time. You are probably going to follow them for three months or so, or you are going to make some determination.

I mean I would say if you have got a patient with a life-threatening arrhythmia, you are probably going to implant the device, have them on some stable medical management, hopefully not including an antiarrhythmic, and then if they have recurrent spells, you are going to have a follow-up period of two or three months to see before you enroll them in a study.

You are not going to say, oh, you have got a life-threatening arrhythmia, I am going to follow you for three months and then decide what I am going to do. You are not going to do that. So, that is a different substrate again.

So, you are probably going to pick up people with life-threatening arrhythmias with an ICD or some form of therapy that they ought to have a history. There should be a history to count back at least a month or two or three.

DR. TRACY: Okay. I think that is right because just as you say, even if you have somebody who doesn't necessarily have a life-threatening arrhythmia, you can't leave them walking around having multiple repetitive events.

You have to do something, so I think if you are going to do this, you are going to be doing it on sicker people, and you will have, just by the point of getting to that time where you are enrolling them in this study where they are acting as their own control, you will have some period of observation.

MS. MOYNAHAN: Let's move on to the next discussion point.

[Slide.]

Question No. 9 is a recap of Question No. 4, which had to do with the duration of the follow-up period. So, unless there are any new issues with the non-randomized study compared to the randomization study, we will just move on.

[Slide.]

Along with the typical inclusion criteria for an ablation study, sponsors are encouraged to include the following. They should specify perhaps a minimum frequency of VT episodes in order to be able to capture a measurable change following ablation.

They should specify whether patients are required

to have an ICD. They should specify the etiology of VT, and since it is not a randomization study, the sponsor does not have to require that patients be amendable to drug therapy. They should specify whether or not patients are drug refractory or intolerant to antiarrhythmic medications.

[Slide.]

We have identified three outcome measures for this type of study. The first is a measure of acute or procedural success, which brings us back to our question of the relevance and definition of acute efficacy and how to assess it.

[Slide.]

Unless there are new issues associated with the non-randomized study, we will just move on.

DR. SIMMONS: I think acute success in a life-threatening VT study is only an observation, and not a primary endpoint.

MS. MOYNAHAN: Not a primary endpoint.

[Slide.]

The second outcome measure is a measure of long-term efficacy, and it could be defined either as a decrease in VT episodes during the follow-up or an absence of VT episodes during the follow-up.

[Slide.]

Question No. 12 is fairly critical to this study